Am J Hum Genet 27:573–585, 1975

Inheritance of Very Low Serum Dopamine-β-Hydroxylase Activity

RICHARD M. WEINSHILBOUM,[1] HELMUT G. SCHROTT,[2] FREDRICK A. RAYMOND,[1] WILLIAM H. WEIDMAN,[3] AND LILA R. ELVEBACK[4]

INTRODUCTION

Dopamine-β-hydroxylase (DBH; E.C.1.14.2.1) is a mixed function oxidase that catalyzes the conversion of 3,4-dihydroxyphenylethylamine (dopamine) to the neurotransmitter norepinephrine [1]. It is localized to catecholamine-containing vesicles in the adrenal medulla and in sympathetic nerves [2, 3], is released with catecholamines in response to stimulation of both sympathetic nerves and the adrenal medulla [4–6], and is present in the blood of humans and experimental animals [7–9]. Serum DBH is biochemically and immunochemically similar to that present in other tissues [8, 10, 11], is elevated in blood obtained from experimental animals under stress [12], and is decreased in blood obtained from rats after partial chemical destruction of sympathetic nerve terminals [13]. These findings have led to the suggestion that serum DBH activity might be a useful measure of the function of the sympathetic nervous system in man [8, 11].

Although serum DBH activity has been measured in patients suffering from many neurological and vascular diseases, the results of these studies have often been contradictory or confusing. One of the reasons for this is a lack of understanding of factors which regulate circulating levels of DBH activity in man. Factors that have been demonstrated to affect human serum DBH activity include age

Received October 11, 1974; revised March 10, 1975.

Portions of these data were presented at the annual meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, May 1974, and at the annual meeting of the American Society of Human Genetics, Portland, Oregon, October 1974.

This work was supported in part by a Faculty Development Award in Clinical Pharmacology to R. M. Weinshilboum from the Pharmaceutical Manufacturers Association Foundation, Inc.; by grants NS 11014, HL 17487-1, and HE 14196E from the National Institutes of Health; and by Minnesota Heart Association grant MHA 12.

[1] Departments of Pharmacology and Internal Medicine, Mayo Foundation, Rochester, Minnesota 55901. Address reprint requests to R. M. Weinshilboum.

[2] Department of Medical Genetics, Mayo Foundation, Rochester, Minnesota 55901. Present address: Lipid Research Clinic, University of Iowa, Iowa City, Iowa 52242.

[3] Department of Pediatrics, Mayo Foundation, Rochester, Minnesota 55901.

[4] Department of Medical Statistics and Epidemiology, Mayo Foundation, Rochester, Minnesota 55901.

[14, 15], transient stress [16, 17], and genetic factors [18, 19]. Because of the apparent importance of heredity in the determination of serum DBH activity, the present investigation of values of circulating DBH activity in a large randomly selected populaton of children, adults, and family members of individuals with very low enzyme activity was carried out. The results of this study are compatible with autosomal recessive inheritance of very low serum DBH activity in man. These results will affect the interpretation of clinical studies in which human serum DBH activity is measured in disease states (e.g., hypertension).

SUBJECTS AND METHODS

Population Sample

Blood was obtained by venipuncture from 841 children between the ages of 6 and 12 at school in the morning after an overnight fast. The population was selected only in so far as it included those children whose parents gave consent. In the schools in which the survey was performed, 87% of the children participated in the study. These 841 children included two black and two Oriental children; the remainder were white. The 1970 census showed that the population of Rochester, Minnesota, includes 0.35% black and 0.88% other nonwhite residents [20].

Blood samples were also obtained from 227 consecutive adult blood donors at the Mayo Clinic in Rochester, Minnesota. All of these subjects were unrelated, white, and reported that they were receiving no medications at the time the blood samples were withdrawn.

Assay Procedure

DBH activity was determined by the method of Molinoff et al. [21] as modified to measure serum enzyme activity [8, 14]. The assay was carried out as previously described [14], except that 1 M acetate buffer, pH 4.92, was substituted for the 1 M Tris-HCl buffer, pH 6.0, to obtain a final reaction mixture pH of 5.2, the optimal pH for DBH activity under these assay conditions. Serum samples heated to 95°C for 5 min were used as blanks, and samples that contained 100 ng of β-phenyl-β-hydroxyethylamine HCl served as a standard for the portion of the reaction catalyzed by phenylethanolamine-*N*-methyltransferase. A known quantity of purified human adrenal DBH was added to selected samples to correct for activation or inhibition of DBH which might occur. All samples were assayed at a 1:50 dilution of serum with glass-distilled water and in the presence of 3 μM $CuSO_4$ to inactivate endogenous inhibitors of the enzyme. One unit (U) of enzyme activity represented the production of 1 nmol of β-phenyl-β-hydroxyethylamine per milliliter of serum per hour of incubation at 37°C. The individual who carried out all assays was unaware of the identity of the subject from whom the sample was obtained.

Purification of Dopamine-β-Hydroxylase

DBH was purified from human adrenal glands obtained at autopsy by a modification of the procedure of Geffen et al. [22]. The DBH obtained by this procedure was stored in the presence of 0.25% bovine serum albumin in 0.05 M Tris-HCl buffer, pH 7.4, to prevent the loss of enzyme activity that occurs when the purified enzyme is stored in the absence of other protein at −20°C [11, 23].

Blood Pressure Determination

The blood pressures of all children who participated in the study were determined by the same two physician observers. The children were seated and the measurement was

made with a mercury sphygmomanometer 5–10 min prior to venipuncture. An appropriate arm cuff was used that covered at least two-thirds of the length of the upper arm without obstructing the elbow or axilla. Systolic blood pressure was measured at the first Korotkoff sound and diastolic at Korotkoff 4 [24]. The value of blood pressure at Korotkoff 5 was also recorded.

Genetic Analysis

Twenty-five families with at least one child with very low serum DBH activity (less than 50 U) had been identified at the time a decision was made to carry out family studies. A proband for a particular family was the oldest sibling in the family with serum DBH activity of less than 50 U who had been discovered in the course of the screening studies. Three of the 25 families (families 44272, 67161, and 73958) were ascertained more than once during the initial screening procedure. Three families did not take part in the investigation: two had moved out of the area and one refused participation. Family histories were taken and pedigrees of the remaining 22 families (88%) were constructed. Among the 22 participating families, 114 of 120 (95%) living first-degree relatives volunteered blood samples. Blood samples were obtained from second-degree relatives in three families in which parents of probands had very low DBH serum enzyme activity and in which relatives lived nearby.

All data were recorded on computer punch cards and stored on magnetic tape for further analysis on a CDC 3500 computer. Standard statistical and genetic methods were used for the evaluation of data.

RESULTS

Population Studies

The frequency distributions of values of serum DBH activity in the 841 children and 227 adult subjects are shown in figure 1. Since this group of children includes many sets of siblings, the frequency distribution in a population of 554 children that includes only one randomly chosen member of each group of siblings is also shown. The distributions for both children and adults are skewed and in both cases include a group of subjects with very low activity (less than 50 U) which may represent a separate subgroup within the population. If the subjects with very low activity are deleted, the skewness of the distribution can be corrected by utilizing the square root of the serum DBH value rather than the value itself.

A total of 3.1% of the adult subjects and 4.7% of the children had enzyme activity of less than 50 U. However, the data for children are influenced by the fact that several sets of siblings with very low serum DBH activity are included among the 841 children studied. The 4.7% represents 40 children from 31 families, including three of three siblings tested in one family, three of four in another family, two of three siblings (two families), and two of two siblings (three families). When only one child was chosen randomly from each sibship tested, 4.3% of the children were included in the group with very low enzyme activity (fig. 1). The striking familial aggregation of very low serum DBH activity and the suggestion that these subjects might compose a separate subgroup of a control population led to the detailed family studies described below.

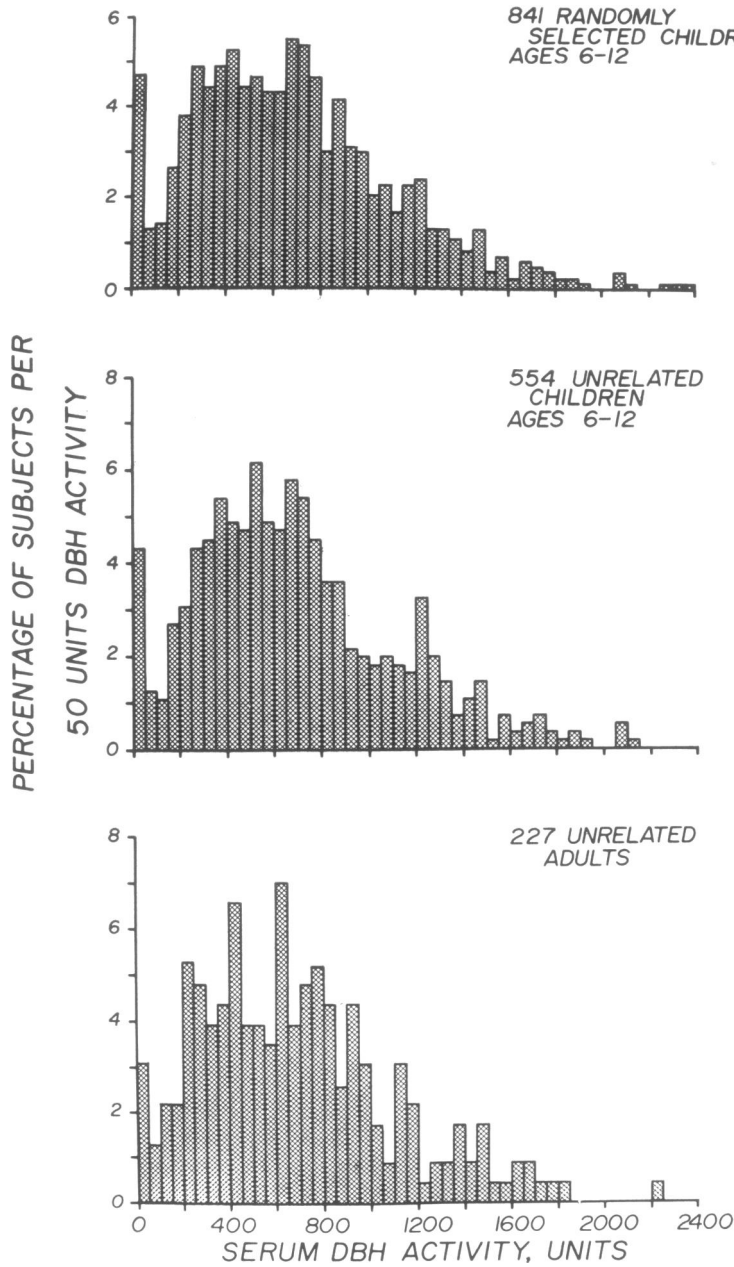

FIG. 1.—Frequency distributions of serum DBH activity in successive 50-U increments for 841 children ages 6–12, 554 of the same children with only one randomly chosen child from each family represented, and 227 unrelated adult subjects.

Inhibition Studies

It is possible that the differences in individual values of DBH activity in human blood might be due to individual variations in circulating levels of activators or inhibitors of the enzyme. Therefore, purified human adrenal DBH was added to randomly selected samples of serum from children with either very low DBH activity (less than 50 U) or high normal activity (600–1,200 U). DBH activity was determined in these samples under the standard assay conditions of dilution and cupric ion concentration (table 1). No significant difference was found be-

TABLE 1

RECOVERY OF PURIFIED HUMAN ADRENAL DBH ACTIVITY FROM HUMAN SERUM

Group	No.	Average DBH Activity	Additional Activity with Added Purified Human Adrenal DBH	% Recovery of Added DBH
Very low	8	14 ± 4	518 ± 21	96 ± 4
High normal	6	876 ± 90	490 ± 70	91 ± 14
Purified human adrenal DBH	12	535 ± 13	...	...

NOTE.—Values shown are mean ± SEM. See text for explanation.

tween the recovery of purified human adrenal DBH assayed in the presence of serum from subjects with very low and high normal DBH activity.

Familial Correlation

We have previously reported a significant sibling-sibling correlation in serum DBH values of 94 sibling-sibling pairs included among the first 317 consecutive children examined in the course of this study [18]. Table 2 presents data on the

TABLE 2

SIBLING CORRELATIONS OF SERUM DBH ACTIVITY

	All Subjects				Excluding Families with Children with DBH < 50 U			
	r_{xy}	r_{xx}	N	P	r_{xy}	r_{xx}	N	P
All siblings	.47	.47	237	<.01	.43	.43	218	<.01
Boy-boy	.35	.34	64	<.01	.45	.44	60	<.01
Girl-girl	.54	.50	64	<.01	.47	.46	58	<.01
Boy-girl	.54	.51	108	<.01	.40	.39	100	<.01
Random pairs nonsiblings	.05	...	182	>.20	.04	...	174	>.20

NOTE.—Interclass (r_{xy}) and intraclass (r_{xx}) correlations of relative deviates from sex-specific regression on age. See text for explanation. N = number of sibling pairs in each category.

correlation of the serum DBH values found in the 237 sets of siblings included among the 841 children studied. All correlations were established in terms of age- and sex-specific relative deviates about sex-specific regressions of the square root of DBH activity on age. The square root transformation was introduced to correct for the skewness of the DBH distributions, and the relative deviates from sex-specific regressions on age to correct for the slight increase of DBH with age in males. The results are expressed as both interclass and intraclass sibling-sibling correlation coefficients between these relative deviates. Random pairs of non-siblings were generated by use of tables of random numbers. All correlation coefficients except those from random pairs were significantly different from zero. There is no evidence of heterogeneity in the correlation coefficients for the boy-boy, boy-girl, and girl-girl pairs. Because of evidence from population studies and from the family studies described below which indicated that subjects with serum DBH activity of less than 50 U might be part of a separate subgroup, the results were also analyzed excluding data on families in which at least one offspring was found to have very low DBH activity. The results were unchanged. However, since ascertainment of subjects with very low DBH activity was incomplete (this study only included children aged 6–12), not all families with children with very low activity were excluded.

Family Studies

Serum DBH activity was measured in relatives of children with very low enzyme activity. The pedigrees of each of the 19 families and three kindreds studied are shown in figure 2.* Although subjects in the 50–99 U range are shown on the pedigrees, all subsequent calculations are based upon the assumption that only individuals with DBH activity of less than 50 U are "affected."

In 16 families (73%), both parents had serum DBH activity greater than 50 U; one parent was affected in five families, and both parents had very low enzyme activity in one family. If very low DBH activity is inherited by a mechanism involving a single gene of large effect, the relative lack of vertical transmission makes dominant inheritance less likely. Because of the equal representation of boys and girls among affected children, sex-linked inheritance is also unlikely.

The possibility of autosomal recessive inheritance of very low serum DBH activity was tested by two different methods of sibship analysis. The "direct a priori method" [25] gave a corrected calculated value for the proportion of affected siblings of probands of .274. Only data from the 16 families in which both parents had serum DBH activity greater than 50 U were used for these calculations. Because this method assumes complete ascertainment, the "Weinberg proband method" [26], which does not assume complete ascertainment, was also used. This method gave an estimate of the sib proportion, $p \pm$ SE, of $.267 \pm .075$, a value that does not differ significantly from the expected value of .25 if inheri-

* See NAPS document no. 02569 for a list of the ages and serum DBH values of each individual represented in figure 2. Order from ASIS/NAPS, % Microfiche Publications, 440 Park Avenue South, New York, New York 10016.

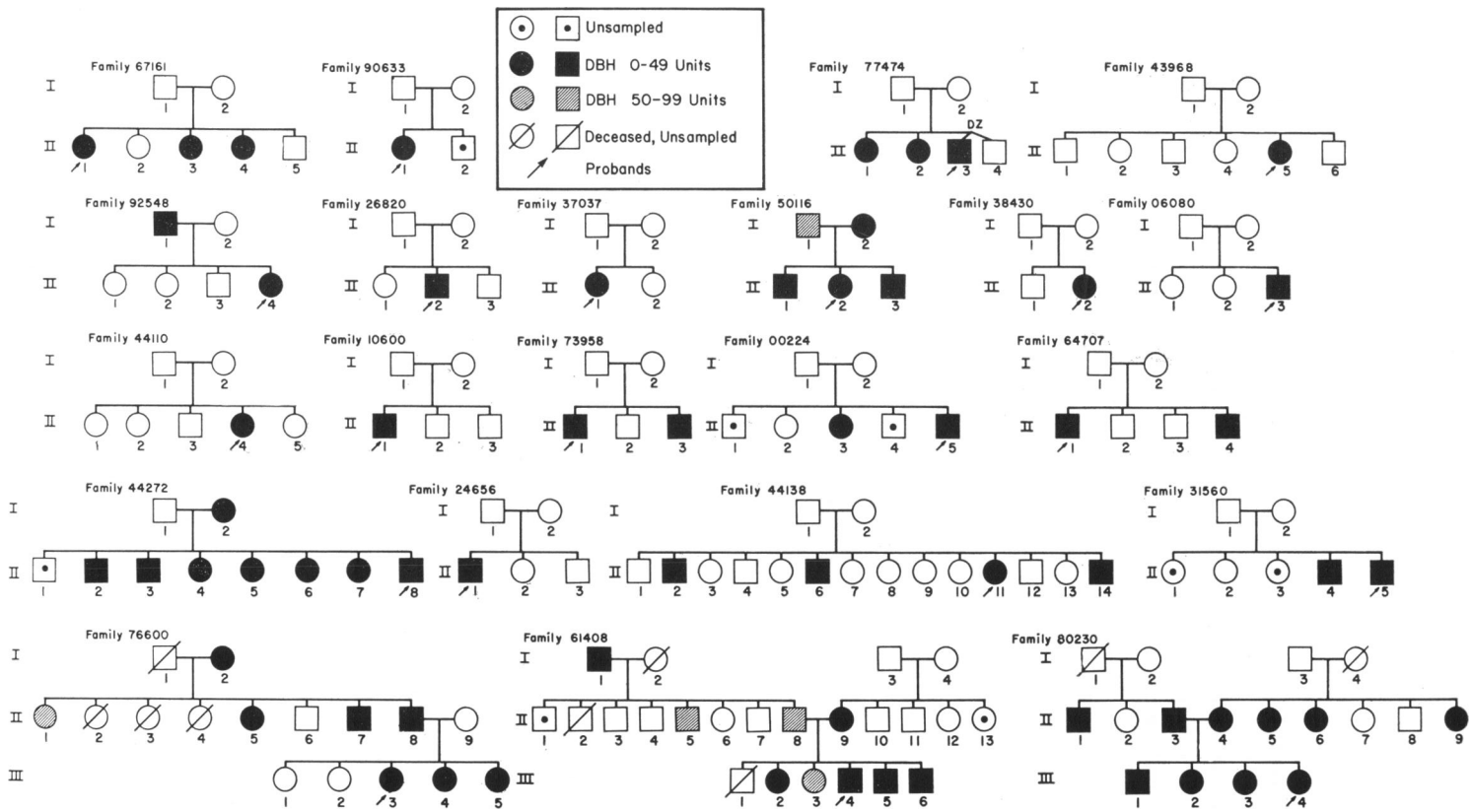

FIG. 2.—Pedigrees of 22 families in which at least one child had very low serum DBH activity (<50 U)

tance is by a recessive mechanism. If autosomal recessive inheritance of very low serum DBH activity occurs, the parents in the 16 families in which both parents had serum DBH activity greater than 50 U would be expected to be heterozygous for the hypothetical recessive allele. The mean value of serum DBH activity for these 32 parents is 518 ± 70 (mean ± SEM) and that of the adult control population is 682 ± 27. Figure 3 shows the cumulative frequency distribution of serum DBH values from 41 parents of children with very low serum DBH activity compared to that from a randomly selected adult control population, excluding subjects with values of less than 50 U ($N = 220$). The two curves differ significantly

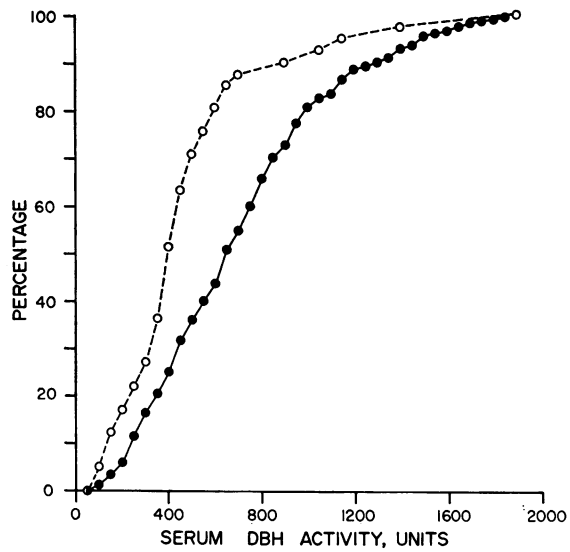

FIG. 3.—Cumulative frequency distribution of serum DBH activity in successive 50-U increments for 220 randomly selected adult subjects (*closed symbols*) and 41 parents of children with very low serum DBH activity (*open symbols*). Individuals with serum DBH activity of less than 50 U have been excluded.

($P < .01$ by the Kolmogorov-Smirnov test [27]). Individuals included in the adult control population with very low serum DBH activity were excluded from consideration to make the control group comparable to the group of parents of probands, but the curves still differ significantly ($P < .01$) even if such subjects are included in the calculations. The distribution of DBH values in siblings of probands in families in which both parents had DBH values of greater than 50 U is shown in figure 4. Of these siblings, 22.9% had very low enzyme activity, and the distribution suggests the existence of another group with a mean enzyme value close to that of the parents of affected children.

Although these data are compatible with autosomal recessive inheritance, polygenic inheritance cannot be entirely excluded. The number of first-degree relatives who might be affected if low serum DBH levels were the result of polygenic inheritance is approximately 20% [28]. Among the 22 families studied, 30% (34/114)

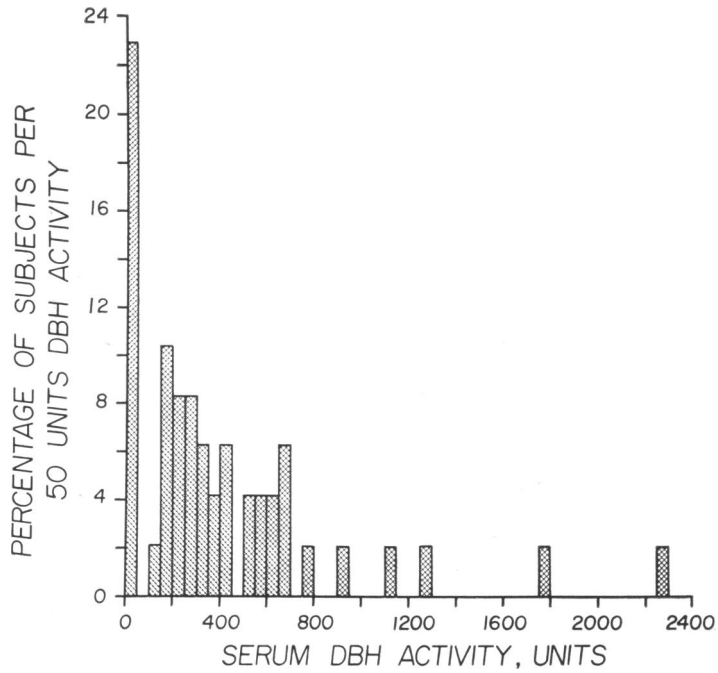

FIG. 4.—Frequency distributions of serum DBH activity in successive 50-U increments for 48 siblings of probands with very low serum DBH activity (< 50 U). Only data from the 16 families in which both parents had activity of greater than 50 U are included.

of first-degree relatives (excluding probands) were affected. This figure is significantly different ($P < .01$) from the expected frequency if the inheritance of low serum DBH activity were polygenic.

Serum DBH and Blood Pressure

There have been many attempts to correlate serum DBH activity with physiologic variables such as blood pressure which are influenced by sympathetic nervous system function. Attempts to demonstrate a significant correlation between serum DBH activity and blood pressure have yielded conflicting results [29, 30]. The existence of genetically different subgroups with different serum DBH values might help to explain some of these results.

Blood pressure measurements were available for 829 of the 841 children. If it is assumed that subjects with serum DBH activity of less than 50 U are homozygous for an allele *d* for very low DBH and that individuals who are heterozygous for this allele have serum enzyme activity intermediate between that found in *dd* and *DD* subjects, comparisons of the distribution of blood pressure values in genetic subgroups are complicated by the overlap of DBH activity between the *DD* and *Dd* groups. Therefore, the population of schoolchildren studied was arbitrarily divided into groups: DBH activity less than 50 U, 50–999 U, 1,000–

1,499 U, and 1,500 U or greater. The mean systolic and diastolic blood pressures of these groups did not differ (table 3). Furthermore, no significant correlation between age- and sex-corrected systolic or diastolic blood pressure values and DBH values was found in these 829 children regardless of whether subjects with serum enzyme values of less than 50 U were included in the calculations. Finally, no significant correlation was found between DBH values and either systolic or diastolic blood pressures within the four groups of children. It should be pointed out, however, that the DBH values for subjects with very low activity, the group most clearly appearing to represent a genetically determined subgroup, are so near the limits of sensitivity of the assay procedure that the DBH measurements are really of value only to assign individuals to this group. It should also be emphasized that these data were obtained from a population of white children between the ages of 6 and 12; the relationship to the situation in adults is unknown.

DISCUSSION

Many clinical studies have been performed in which serum dopamine-β-hydroxylase activity has been measured. Results have frequently been inconclusive or contradictory. One reason may be the important role that familial factors play in the determination of serum DBH activity: a significant sibling-sibling correlation of serum DBH values has been reported [18]; studies carried out in twins have demonstrated a higher degree of correlation of serum DBH activity in monozygotic than in dizygotic twins [19]; and several investigators have noticed familial aggregation of very low serum DBH values [14, 29]. Evidence has been presented here that subjects with very low serum DBH activity (less than 50 U) make up a separate subgroup within a randomly selected population. Although polygenic inheritance of very low enzyme activity cannot be excluded, several lines of evidence support monogenic inheritance by an autosomal recessive mechanism. First, the results of sibship analysis are compatible with a recessive pattern of inheritance. Second, the frequency distribution of serum enzyme activity among siblings of affected children suggests at least two populations of values, one mode for affected (less than 50 U) and one for subjects with values similar to those of

TABLE 3

BLOOD PRESSURE BY DBH SUBGROUP

DBH ACTIVITY	No.	BLOOD PRESSURE	
		Systolic	Diastolic
<50	40	113.0 ± 10.5	70.8 ± 7.1
50–999	620	113.5 ± 11.7	71.3 ± 8.5
1,000–1,499	134	114.6 ± 12.2	72.1 ± 8.1
≥1,500	35	111.4 ± 13.7	70.2 ± 10.3

NOTE.—Values (mean ± SD) shown for 829 children tested.

unaffected parents of affected children. Finally, in most of the families studied there is a paucity of vertical transmission with the parents being unaffected. These results are compatible with autosomal recessive inheritance. Individuals heterozygous for the recessive allele appear to have circulating enzyme activity intermediate between that found in homozygotes and in a control population. Such a model does not exclude the possibility that other familial factors either due to genetic or environmental influences might also affect serum DBH activity.

Among the possible mechanisms by which genetic factors might act to influence human serum DBH activity are genetically mediated differences in the structure of the enzyme molecule, differences in the quantity of DBH present in tissues, differences in the binding of DBH to the vesicle (i.e., the proportion of "releasable" DBH), differences in the rate of release of enzyme from tissues, differences in the access of enzyme protein to the circulation, and differences in the rate of clearance of the enzyme activity from the blood. Many of these mechanisms can be tested experimentally.

The role of genetic factors in the determination of serum DBH activity has important implications in the interpretation of the results of clinical studies. Serum DBH activity in patients with familial dysautonomia, Down syndrome, and Parkinson disease has been reported to be decreased compared to that found in control subjects [14, 31, 32]. Enzyme activity has been reported to be increased in some studies of hypertensive patients, in one type of torsion dystonia, and in some patients with neuroblastoma [30, 33, 34]. Unless the control groups chosen for these studies are from a genetically comparable population, the results must be interpreted with caution.

It has been suggested that levels of circulating DBH activity might reflect the level of function of the sympathetic nervous system in man. Because of the great variation in baseline levels of enzyme activity, due in large part to genetic factors, a single isolated measurement of DBH activity is not helpful in the determination of the level of sympathetic nervous system function in an individual. Finally, it might be hoped that serum DBH activity would reflect the activity of this important catecholamine biosynthetic enzyme in human neural tissue. Unfortunately, there are so many sources of potential variation between tissue DBH levels and the levels of enzyme activity found in the circulation that it is not possible at present to extrapolate from one to the other.

SUMMARY

Serum dopamine-β-hydroxylase (DBH) activity was measured in blood samples obtained from 841 children ages 6–12, 227 adult subjects, and 114 relatives of children with serum DBH activity of less than 50 units. Approximately 4% of the children and 3% of the adult subjects tested had very low serum DBH activity (50 units or less). Because these subjects appeared to make up a separate subgroup within the population and because of a striking familial aggregation of subjects with very low enzyme activity, serum DBH activity was measured in blood obtained from members of 22 families of probands with very low serum

enzyme activity. The results of sibship and pedigree analyses of the data were compatible with autosomal recessive inheritance of very low serum DBH activity. Unaffected parents of probands had serum DBH activity intermediate between that found in affected individuals and in a control population. No significant correlation of serum DBH activity with either systolic or diastolic blood pressure was found in this randomly selected population of children.

ACKNOWLEDGMENTS

We thank Patricia Hodgson, Joel Dunnette, and Luanne Olson for their assistance.

REFERENCES

1. KAUFMAN S, FRIEDMAN S: Dopamine-β-hydroxylase. *Pharmacol Rev* 17:71–100, 1965
2. OKA K, KAJIKAWA K, OHUCHI T, YOSHIDA H, IMAIZUMI R: Distribution of dopamine-β-hydroxylase in subcellular fractions of adrenal medulla. *Life Sci* [I] 6:461–465, 1967
3. STJÄRNE L, LISHAJKO F: Localization of difference steps in noradrenaline synthesis to different fractions of a bovine splenic nerve homogenate. *Biochem Pharmacol* 16:1719–1728, 1967
4. GEFFEN LB, LIVETT BG, RUSH RA: Immunological localization of chromogranins in sheep sympathetic neurons, and their release by nerve impulses (abstr.). *J Physiol* (Lond) 204:58P–59P, 1969
5. DE POTTER WP, DE SCHAEPDRYVER AF, MOERMAN EJ, SMITH AD: Evidence for the release of vesicle-proteins together with noradrenaline upon stimulation of the splenic nerve (abstr.). *J Physiol* (Lond) 204:102P–104P, 1969
6. VIVEROS OH, ARQUEROS L, KIRSHNER N: Release of catecholamines and dopamine-β-hydroxylase from the adrenal medulla. *Life Sci* [I] 7:609–618, 1968
7. WEINSHILBOUM R, AXELROD J: Dopamine-β-hydroxylase activity in human blood (abstr.). *Pharmacologist* 12:214, 1970
8. WEINSHILBOUM R, AXELROD J: Serum dopamine-β-hydroxylase. *Circ Res* 28:307–315, 1971
9. GOLDSTEIN M, FREEDMAN LS, BONNAY M: An assay for dopamine-β-hydroxylase activity in tissues and serum. *Experientia* 27:632–633, 1971
10. ROSS SB, WEINSHILBOUM R, MOLINOFF PB, VESELL ES, AXELROD J: Electrophoretic properties of dopamine-β-hydroxylase in several tissues from three species. *Mol Pharmacol* 8:50–58, 1972
11. RUSH RA, GEFFEN LB: Radioimmunoassay and clearance of circulating dopamine-β-hydroxylase. *Circ Res* 31:444–452, 1972
12. WEINSHILBOUM RM, KVETNANSKY R, AXELROD J, KOPIN IJ: Elevation of serum dopamine-β-hydroxylase activity with forced immobilization. *Nature* [*New Biol*] 230:287–288, 1971
13. WEINSHILBOUM R, AXELROD J: Serum dopamine-β-hydroxylase: decrease after chemical sympathectomy. *Science* 173:931–934, 1971
14. WEINSHILBOUM R, AXELROD J: Reduced plasma dopamine-β-hydroxylase activity in familial dysautonomia. *N Engl J Med* 285:938–942, 1971
15. FREEDMAN LS, OHUCHI T, GOLDSTEIN M, AXELROD F, FISH I, DANCIS J: Changes in human serum dopamine-β-hydroxylase activity with age. *Nature* (Lond) 236:310–311, 1972
16. WOOTEN GF, CARDON PV: Plasma dopamine-β-hydroxylase activity: elevation in man during cold pressor test and exercise. *Arch Neurol* 28:103–106, 1973

17. PLANZ G, PALM D: Acute enhancement of dopamine-β-hydroxylase activity in human plasma after maximum work load. *Eur J Clin Pharmacol* 5:255–258, 1973
18. WEINSHILBOUM RM, RAYMOND FA, ELVEBACK LR, WEIDMAN WH: Serum dopamine-β-hydroxylase activity: sibling-sibling correlation. *Science* 181:943–945, 1973
19. ROSS SB, WETTERBERG L, MYRHED M: Genetic control of plasma dopamine-β-hydroxylase. *Life Sci* [I] 12:529–532, 1973
20. UNITED STATES DEPARTMENT OF COMMERCE, BUREAU OF THE CENSUS: *General Population Characteristics: Minnesota,* Washington, D.C., Government Printing Office, 1970
21. MOLINOFF PB, WEINSHILBOUM R, AXELROD J: A sensitive enzymatic assay for dopamine-β-hydroxylase. *J Pharmacol Exp Ther* 178:425–431, 1971
22. GEFFEN LB, LIVETT BG, RUSH RA: Immunohistochemical localization of protein components of catecholamine storage vesicles. *J Physiol* (Lond) 204:593–605, 1969
23. WEINSHILBOUM RM, THOA NB, JOHNSON DG, KOPIN IJ, AXELROD J: Proportional release of norepinephrine and dopamine-β-hydroxylase from sympathetic nerves. *Science* 174:1349–1351, 1971
24. Moss AJ, ADAMS FH: Index of indirect estimation of diastolic blood pressure. *Am J Dis Child* 106:364–367, 1963
25. LI CC: *Human Genetics.* New York, McGraw-Hill, 1961
26. CAVALLI-STORZA LL, BODMER WF: *The Genetics of Human Populations.* San Francisco, Freeman, 1971
27. LINDGREN BW, MCELRATH GW: *Introduction to Probability and Statistics.* New York, Macmillan, 1959
28. EDWARDS JH: Familial predisposition in man. *Br Med Bull* 25:58–64, 1969
29. HOROWITZ D, ALEXANDER W, LOVENBERG W, KEISER HR: Human serum dopamine-β-hydroxylase: relationships to hypertension and sympathetic activity. *Circ Res* 32:594–599, 1973
30. SCHANBERG SM, STONE RA, KIRSHNER N, GUNNELS JC, ROBINSON RR: Plasma dopamine-β-hydroxylase: a possible aid in the study and evaluation of hypertension. *Science* 183:523–525, 1974
31. WETTERBERG L, GUSTAVSON K-H, BÄCKSTRÖM M, ROSS SB, FRÖDEŃ O: Low dopamine-β-hydroxylase activity in Down's syndrome. *Clin Genet* 3:152–153, 1972
32. LIEBERMAN AN, FREEDMAN LS, GOLDSTEIN M: Serum dopamine-β-hydroxylase activity in patients with Huntington's chorea and Parkinson's disease. *Lancet* 1:153–154, 1972
33. WOOTEN GF, ELDRIDGE R, AXELROD J, STERN RS: Elevated plasma dopamine-β-hydroxylase activity in autosomal dominant torsion dystonia. *N Engl J Med* 288: 284–287, 1973
34. GOLDSTEIN M, FREEDMAN LS, BOHUON AC, GUERINOT F: Serum dopamine-β-hydroxylase activity in neuroblastoma. *N Engl J Med* 286:1123–1125, 1972